UNMASKING OF THE INTRINSIC NEGATIVE INOTROPIC EFFECT OF VASODILATORS: A NEW METHOD USING PHARMACOLOGIC PROBES

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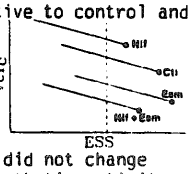
Secondary sympathetic activation with vasodilating agents can mask these drugs' intrinsic negative inotropic effect. Accordingly, we developed a new method to assess LV contractility independent of load and reflex sympathetic changes. 14 non-ischemic hypertensive pts (mean BP=124±14 Hg) were studied using echo-Doppler while on placebo and 1 wk after therapy with nifedipine (Nif). LV end systolic stress (ESS) - rate corrected velocity of shortening (Vcfc) relations were generated over a range of loads induced by nipride. Contractility was assessed using Vcfc at a common LV afterload. At each study, data were acquired before and during IV esmolol (Esm) to determine the presence of significant reflex cardiac sympathetic responses. The adequacy of β-blockade was assessed with isuprel. Nifedipine alone ↑ed mean BP by 15%, SVR by 25% and ESS by 22% while ↑ing HR by 11% and CI by 13% [all p<.001 vs pre-Nif control (Ctl)]. LV contractility changes relative to control and esmolol alone data were:

Contractility	NIF	NIF+ESM
↑	10/14*	2/14
NC	2/14	1/14
↓	2/14	11/14‡

*p<.05 ‡p<.001



In 12/14 pts, nifedipine augmented or did not change contractility. Ablation of reflex sympathetic activity with esmolol unmasked nifedipine's negative inotropic effect in 9/14 pts. Thus, this noninvasive technique can be used to isolate intrinisic contractility changes in drugs with combined vasodilator and inotropic action.

INFLUENCE OF INOTROPIC AGENTS ON LEFT VENTRICULAR CONTRACTILITY AND MYOCARDIAL ENERGETICS IN PATIENTS WITH DILATED CARDIOMYOPATHY

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Left ventricular contractile state and energy conversion efficiency were investigated in 11 patients with dilated cardiomyopathy, using left ventricular pressure-volume relation before and after administration of dobutamine(DOB) and oral phosphodiesterase inhibitor(MS-857). Pressure-volume area(PVA), external work(EW), end-systolic elastance(Ees), and effective arterial elastance(Ea) were measured using continuous pressure-volume diagram obtained by a conductance catheter. Myocardial oxygen consumption (MVO_2) was measured using coronary sinus flow and oxygen difference from a coronary sinus catheter.

After administration of MS-857 and DOB, significant increase in Ees(1.00 to 1.35 mmHg/ml after MS-857, and 1.12 to 1.54 after DOB), decrease in Ea(2.75 to 2.35 mmHg/ml after MS-857, and 2.45 to 2.15 after DOB), and decrease in Ea/Ees (3.15 to 2.07 after MS-857, and 2.84 to 1.54 after DOB) toward a so called optimal ventriculoarterial coupling were observed. As a result, EW/PVA efficiency increased from 33 to 40% after MS-857 and from 34 to 42% after DOB.

Both energy conversion efficiency PVA/MVO_2 and EW/MVO_2 had a inverse relation to Ees(r=-0.81 and r=-0.78, p<0.05), while EW/PVA increased with Ees(r=0.66,p<0.05). In conclusion, inotropic agents increase contractility and external work efficiency, but have a possibility of oxygen wasting effect in patients with dilated cardiomyopathy.

IS ATROPHY A FORM OF CARDIAC ADAPTATION? A STUDY OF PATIENTS WITH CHRONIC SPINAL CORD INJURY

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To test the hypothesis that sympathetic denervation and decreased systolic load can result in reduced LV mass and/or remodeled LV architecture, 14 quadriplegic men with spinal cord injury (SCI, 29-66 yrs) and 14 age-matched normal men (N, 30-74 yrs) were studied. Duration of injury in SCI was 3-542 mos., mean 188 mos.; injury levels C3-C8. Activity level, based on an interview score of 0=ventilator dependent, 5=normal, averaged 2.0 in SCI. Two-dimensional echoes and Doppler recordings of LV inflow and aortic flow were digitized for LV mass, volume (single plane Simpson's rule), mean wall thickness (h), and flow velocity.

LV mass index (LVMI) was significantly lower in SCI than in N (78+-10 vs 95+-7 g/m2, p=.001). LV end-diastolic and end-systolic volumes and h were the same in both groups, although CO (4.3+-1 vs 5.1+-.7 L/min), stroke volume (69+-13 vs 79+-12 ml), and LA size (3.2+-.5 vs 3.7+-.4 cm) were reduced in SCI (p<.05). In spite of reductions in LVMI, LV chamber architecture, as described by relative wall thickness ratio, mass/volume ratio and short/long LV axis ratio, was normal. Resting supine systolic and diastolic blood pressures (BP) were lower in SCI (103+-17 vs 127+-9 and 61+-13 vs 76+-7 mmHg, both p=.001) and LV end-systolic circumferential wall stress was reduced (143+-44 vs 177+-34 kd/cm2, p=.03). Ejection fraction and LV filling pattern were similar in both groups. SCI had shorter aortic ejection times (.29+-.04 vs .38+-.09 sec, p=.003) and longer acceleration time to ejection time ratios (.35+-.07 vs .28+-.06, p=.01) suggestive of mild systolic dysfunction. Independent correlates of reduced LVMI in SCI in a stepwise regression model were: decreased activity, lower systolic BP and advanced age (r=.85, p=.003 overall). Patient injury level, injury duration and wall stress were not significant.

Thus, diminished activity and reduced blood pressure may play an important role in the down regulation of LVMI even in the absence of hypertrophy. LV remodeling occurred in such a way that normal chamber shape, architecture, and diastolic filling were maintained, while systolic function may have been minimally impaired. These findings suggest that atrophy, similar to hypertrophy, is a form of cardiac adaptation.

ATRIAL NATURIURETIC FACTOR NORMALIZES FILLING PRESSURES, URINE FLOW RATE AND SODIUM LEVELS IN END-STAGE HEART FAILURE

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In order to measure the hemodynamic and renal effects of atrial natriuretic factor (ANF), we infused ANF at 0.01, 0.03 and 0.1 ug/kg/min for 45 min at each dose in 5 class IV heart failure (CHF) and 5 normal (N1) subjects during continuous hemodynamic monitoring. Plasma ANF levels increased similarly in both groups (N1: 24±5 to 1105±147, CHF: 117±22 to 1470±158 pg/ml P<0.001 for both) and were associated with significant falls in RA pressure (N1: -3.6±0.2 CHF: -6.5±1.6 mmHg), mean PA pressure (N1: -5.2 ±0.3, CHF: -13.5±3.1) and pulmonary capillary wedge pressures (PCWP) (N1: -5.1±0.6, CHF: -12.7±2.1) (all p<0.001) at the highest dose. The final filling pressures in CHF (RA: 5.7± 2.8, PCWP 11.1±3.5 mmHg) were similar to the initial pressures in N1 (RA: 6.0±2.1, PCWP 9.8±3.6 mmHg, P=NS for both). Urine flow rate rose significantly in both groups (N1: 6.6±1.2 to 25.7±6.3 ml/min, CHF: 2.2±0.6 to 7.1±3.4, p<0.05 for both). Urine sodium loss rose in a similar significant fashion (n1: 211±19 to 1367±179 and CHF: 17±4 to 232±73 uEg/min p<0.05 for both).

We conclude that the hemodynamic, diuretic and natriuretic effects of ANF are favorable and can normalize the baseline abnormalities that exist in end-stage heart failure.